A Novel Pain Management Strategy for Combat Casualty Care

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See editorial, p. 128.

Study objective: Pain control in trauma patients should be an integral part of the continuum of care, beginning at the scene with out of hospital trauma management, sustained through the evacuation process, and optimized during hospitalization. This study evaluates the effectiveness of a novel application of a pain control medication, currently indicated for the management of chronic and breakthrough cancer pain, in the reduction of acute pain for wounded Special Operations soldiers in an austere combat environment.

Methods: Doses (1,600 μg) of oral transmucosal fentanyl citrate were administered by medical personnel during missions executed in support of Operation Iraqi Freedom from March 3, 2003, to May 3, 2003. Hemodynamically stable casualties presenting with isolated, uncomplicated orthopedic injuries or extremity wounds who would not have otherwise required an intravenous catheter were eligible for treatment and evaluation. Pretreatment, 15 minute posttreatment, and 5 hour posttreatment pain intensities were quantified by the verbal 0 to 10 numeric rating scale.

Results: A total of 22 patients, aged 21 to 37 years, met the study criterion. The mean difference in verbal pain scores (5.77; 95% confidence interval [CI] 5.18 to 6.37) was found to be statistically significant between the mean pain rating at 0 minutes and the rating at 15 minutes. However, the mean difference (0.39; 95% CI −0.18 to 0.96) was not statistically significant between 15 minutes and 5 hours, indicating the sustained action of the intervention without the need for redosing. One patient experienced an episode of hypoventilation that resolved readily with administration of naloxone. Other documented adverse effects were minor and included pruritus (22.7%), nausea (13.6%), emesis (9.1%), and lightheadedness (9.1%).

Conclusion: Oral transmucosal fentanyl citrate can provide an alternative means of delivering effective, rapid onset, and noninvasive pain management in an out of hospital, combat, or austere environment.

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Editor's Capsule Summary

What is already known on this topic

There are fewer options for relief of pain in the battlefield setting than in routine medical care.

What question this study addressed

This study examined the use of self administered oral trans mucosal fentanyl citrate among 22 US casualties of the invasion of Iraq.

What this study adds to our knowledge

Oral transmucosal fentanyl citrate was easy to administer and provided rapid analgesia, and adverse effects were few.

How this might change clinical practice

Although very preliminary, this evidence suggests that oral transmucosal fentanyl may be a useful analgesic treatment in the battlefield environment.

INTRODUCTION

Pain is the most common symptom for which people seek medical attention.[1] Optimal management of severe pain in a traditional hospital setting can in itself be a challenging process.[1-4] Attempting to manage pain in an out-of-hospital, combat, or austere environment can be even more demanding.[5-9]

Opiates have long been the mainstay of treatment for moderate to severe pain.[2,3,9,10] In the form of pills, capsules, or tablets, opiates can typically require 20 to 30 minutes to initiate pain relief. Liquids are limited by a notable first-pass metabolism and by packaging and administration restrictions imposed by a field environment. Transdermal patches can be suboptimal because of their delay in pain relief. Intramuscular or subcutaneous opiates can be inadequate because of uncertainty of absorption. Given these limitations, intravenous morphine is recommended for casualties requiring analgesia in combat.[6,7,9] Intravenous morphine can provide rapid onset of analgesia and effective titration of dosage. However, insertion of a simple intravenous catheter can often be delayed by tactical requirements and environmental limitations.[6,7,11]

Soldiers conducting airborne and ground missions in Afghanistan were injured in harsh and hostile environments, often during darkness. Injuries and pain were aggravated during delays in evacuation, followed by prolonged aerial evacuation through enemy airspace in darkened aircraft operating at low altitude, with frequent evasive aerial maneuvers. These combat experiences prompted consideration of alternatives to traditional modalities of pain management for missions in Iraq. Oral transmucosal fentanyl citrate is one alternative that was evaluated. This study describes the use of oral transmucosal fentanyl citrate in combat, characterizes the medication's effect, and reports adverse effects that were encountered.

METHODS

Theoretical Model of the Problem

Before the current conflict in Iraq, several Special Operations physicians had already instituted the protocol of providing each soldier with a "wound pack" of oral medications containing acetaminophen, rofecoxib, and a fluoroquinolone. Soldiers were instructed to take these medications if wounded to decrease the pain associated with injuries and to reduce the risk of wound infection.[12] With this protocol in place, some patients self-treated with first-line pain medications before evaluation by a medical provider. If a patient was still experiencing pain on presentation to a medical provider, additional pain management needs had to be met, and soldiers were historically given intravenous morphine.

Optimally, however, the analgesic agent would be provided orally, possess a good safety profile with minimal adverse effects, be rapid in onset, and be self-administrable, all characteristics of oral transmucosal fentanyl citrate. Oral transmucosal fentanyl citrate administered over a 15-minute period reaches maximal serum levels after 10 to 20 minutes. The mechanism of action of oral transmucosal fentanyl citrate is transmucosal and gastrointestinal. Oral transmucosal fentanyl citrate is rapidly absorbed through the oral mucosa and has a 5- to 10-minute onset of action. However, only 25% of the total dose is absorbed through the oral mucosa. The remaining medication is swallowed and absorbed through the intestinal mucosa. There is a significant first-pass metabolism, with only one third of the swallowed dose reaching the systemic circulation (25% of the total), which gives a total functional absorbed dose of 50% of the administered preparation.

Study Design, Setting, and Data Collection and Processing

This study documents results from a clinical practice guideline instituted during Operation Iraqi Freedom. Criteria were established to use, observe, and monitor the effectiveness of oral transmucosal fentanyl citrate in Special Operations soldiers in a combat environment from March 3, 2003, to May 3, 2003. Oral transmucosal fentanyl citrate in 1,600-μg doses was included in the aid bags of medical officers and senior paramedics conducting initial entry missions, follow-on missions, and combat

casualty evacuation operations during Operation Iraqi Freedom. Because oral transmucosal fentanyl citrate is a schedule II narcotic, precautions similar to those for intravenous morphine were instituted to account for each dose and to minimize the potential for abuse.

Hemodynamically stable soldiers presenting with isolated, uncomplicated orthopedic injuries or extremity wounds that would not have otherwise required an intravenous catheter were immediately asked to verbally rate their pain intensity on a 0-to-10 numeric rating scale,[2,5] with 0 representing no pain and 10 representing the worst possible pain. Soldiers reporting a pain score greater than 5 were provided one 1,600-μg dose of oral transmucosal fentanyl citrate over a 15-minute period and asked to rate their pain at the 15-minute mark and again at 5 hours. The numeric rating scale was used because of its discriminatory power and reliability in trauma patients,[13] as well as its relative ease of use for pain intensity assessment in a dark, hostile environment.

Patients were afforded the opportunity to self-administer the medication, as well as to discontinue the medication once adequate pain control was reached or if undesirable adverse effects occurred. All patients were evaluated and monitored by medical personnel before, during, and continually after administration of the medication, which included frequent monitoring of vital signs and pulse oximetry testing, in addition to direct observation by medical personnel. Data were collected and compiled by the authors, who were the treating providers, after the completion of each mission. Data included pain ratings, vital signs, adverse effects, and patient demographics. Every attempt to collect all data points was made. Individuals with missing data points were included and assimilated appropriately, with no data entered for missing data points.

Initial approval for the conduct of this clinical practice guideline was obtained from the task force surgeon after detailed open-forum discussions among medical and nonmedical personnel. Patient education was provided, and verbal consent was obtained from each patient before administration of the medication, as the tactical scenario permitted. After redeploying to the United States, the authors received approval to conduct a retrospective review of medical documentation from the institutional review boards at the University of Texas Medical Branch, Galveston, TX, and the Uniformed Services University of the Health Sciences, Bethesda, MD. Patient identifiers and protected health information remained secure, and the information was adequately destroyed at the earliest opportunity, consistent with the conduct of the study.

Statistical analysis was accomplished using medians, means, SDs, and confidence intervals (CIs).

RESULTS

Sixty-nine injured soldiers were evaluated during the study, with 42 injuries sustained during airborne assaults and the remainder from ground assaults. A total of 22 male patients, mean age 26 years (range 21 to 37 years), met the conditions of the study (Table). There were no violations of the guideline criteria. Of these 22 patients, none had self-medicated with the oral wound pack, 21 received only one 1,600-μg oral transmucosal fentanyl citrate dose, 1 received two 1,600-μg oral transmucosal fentanyl citrate doses, and 3 required the addition of intravenous medication for pain relief.

The effect of oral transmucosal fentanyl citrate on subjective pain was notable (Figure). The mean difference in verbal pain scores (5.77; 95% CI 5.18 to 6.37) was statistically significant between the mean pain rating at 0 minutes and the rating at 15 minutes. However, the mean difference (0.39; 95% CI −0.18 to 0.96) was not statistically significant between 15 minutes and 5 hours, indicating the sustained action of the intervention without the need for redosing. Because of the asymmetric distribution of values, nonparametric testing through the Wilcoxon signed rank test was also conducted for pairwise comparison of medians, producing similar results.

Complete data retrieval was obtained at baseline and at 15 minutes for all 22 patients. Four patients had incomplete data at 5 hours. The initial pain relief experienced continued without the need for additional analgesic medications for 19 of 22 patients. Of the 3 patients who required further pain relief, 1 received a second dose of oral transmucosal fentanyl citrate and intravenous morphine and phenergan, 1 received intravenous morphine and phenergan, and 1 received intravenous morphine and valium.

Adverse effects were documented in 9 patients. Transient hypoventilation, the one major adverse effect, occurred at the 4-hour mark in the patient who required 2 oral transmucosal fentanyl citrate doses and intravenous medication for pain relief. This adverse effect occurred only after additional intravenous narcotics were provided. The adverse effect was rapidly identified and reversed readily with low-dose naloxone. There was no long-term morbidity associated with this event. Other adverse effects were minor and occurred within 5 to 30 minutes of medication administration, depending on the individual.

These adverse effects consisted of pruritus (22.7%), nausea (13.6%), emesis (9.1%), and lightheadedness (9.1%). The one patient who experienced nausea, emesis, and lightheadedness discontinued the medication before completion.

DISCUSSION

Fentanyl citrate is a highly lipophilic synthetic phenylpiperidine derivative that is approximately 100 times more potent than morphine and selectively binds to the μ-1 and μ-2 receptors. Fentanyl has been used parenterally since the early 1960s. An oral transmucosal formulation was initially approved in 1993 by the US Food and Drug Administration (FDA) for use as Oralet, which was later voluntarily withdrawn from the market. In 1998, an almost identical preparation, Actiq, was also approved by the FDA. Actiq is manufactured by Cephalon (West Chester, PA) using a new compressed powder formulation incorporated into a sweetened raspberry-flavored white lozenge on a stick, which was approved by the FDA in 2003.

Absorption through the oral mucosa is responsible for oral transmucosal fentanyl citrate's rapid onset, whereas the swallowed preparation accounts for the duration effect. The terminal half-life is 6 to 7 hours, and serum concentration increases dose dependently. Fentanyl provides effects ranging from analgesia at blood levels of 1 to 2 ng/mL to surgical anesthesia and profound respiratory depression at levels of 10 to 20 ng/mL. The maximum concentration of 1,600-μg oral transmucosal fentanyl citrate was 2.51 ng/mL in clinical efficacy trials.[14] However, it is important to note that fentanyl is capable of producing respiratory depression at recommended dosages in opiate-intolerant individuals. Oral transmucosal fentanyl citrate undergoes metabolism in the liver and

Table.
Distribution of injuries.

			Subjective Pain				
Casualty No.	**Mechanism**	**Injury**	**0 Min**	**15 Min**	**5 h**	**Other Medications**	**Adverse Effects**
1	Airborne assault	Acute upper back strain	6	1	Missing		Nasal pruritus
2	Airborne assault	Grade III ankle sprain	6	0	Missing		Nasal pruritus
3	Airborne assault	Patellar contusion	6	0	Missing		Nausea, emesis, lightheadedness
4	Airborne assault	Midfoot ligament strain	7	0	0		
5	Airborne assault	Tibia/fibula fracture and dislocation	9	0	0		
6	Airborne assault	Medial malleolar fracture	7	0	0		
7	Airborne assault	Grade III medial collateral ligament sprain	7	0	0		
8	Airborne assault	Left ankle fracture/right ankle sprain	7	0	0		
9	Airborne assault	Transient compartment syndrome	6	0	0		
10	Airborne assault	Ankle fracture	6	1	1		
11	Airborne assault	Acute lower back pain	7	2	2		
12	Airborne assault	2 4 Metatarsal fractures	7	1	1		
13	Airborne assault	Tibia/fibula fracture and dislocation	10	4	1	IV morphine, IV phenergan	Nausea, lightheadedness
14	Airborne assault	Knee dislocation and total disruption	10	5	Missing	Second dose of OTFC, IV morphine, IV phenergan	Hypoventilation
15	Airborne assault	Foot fracture	6	1	1		
16	Airborne assault	Foot injury	6	0	0		
17	Airborne assault	Ankle fracture	6	1	1		
18	Airborne assault	Ankle fracture	8	4	4		Pruritus
19	Airborne assault	Tibia/fibula fracture	8	4	4		Pruritus
20	Airborne assault	2 5 Metatarsal fractures	7	3	3		Pruritus
21	Ground assault	Knee contusion and sprain	8	0	0		Nausea, emesis
22	Ground assault	Acute low back pain	8	4	0	IV morphine, IV valium	

IV, Intravenous; **OTFC,** oral transmucosal fentanyl citrate.

intestinal mucosa by the cytochrome P450 3A4 isozyme to an inactive metabolite, norfentanyl.

Numerous studies have been conducted on adults and children using oral transmucosal fentanyl citrate for procedural pain control and pain control in the preoperative and postoperative period.[15-28] Studies have also been conducted to support the current FDA-approved indication for Actiq, which is for opiate-dependent breakthrough pain in cancer patients.[29-33] All of these studies report on the ability of oral transmucosal fentanyl citrate to effectively provide opiate analgesia with minor adverse effects. In 1991, Lind et al[34] published a report on the use of oral fentanyl citrate for severe pain in emergency departments (EDs). Although oral transmucosal fentanyl citrate was recommended for wilderness medical support by Weiss[8] in 1999, we have found no other studies conducted with oral transmucosal fentanyl citrate in the out-of-hospital setting.

In this study, oral transmucosal fentanyl citrate appeared to bridge the gap in pain control for a specific subset of casualty patients who would have otherwise received intravenous opiate analgesia, which allowed medical providers to focus their attention on the most severely injured patients while providing adequate pain control to less severely injured patients. The current practice for Special Operations forces in the treatment of hemodynamically stable patients is to forgo intravenous fluids.[6,7,35,36] The described noninvasive method of oral transmucosal fentanyl citrate pain control fits well with this practice. Front-line medical personnel carry intravenous fluids, medications, and adjunct materials limited in selection and quantity by their aid bags and the mission template. Thus, intravenous resources in combat are best reserved for hemodynamically unstable patients who require intravenous resuscitation to sustain life.

In our experience, the lozenge-on-a-stick design facilitated patient self-administration, served as a visual indicator that medication was being administered, permitted quick retrieval of the lozenge once adequate pain relief was obtained, and reduced the potential for choking. Taping the stick to the patient's index finger can reduce the risk of inadvertent overmedication, because the patient must remain alert enough to actively self-administer the medication. Accidental swallowing of the preparation was an initial concern that we thought was mitigated by the preparation's design and inherent pharmacodynamic properties. The significant first-pass metabolism lowers the serum concentration to 25% to 33% of the total swallowed dose. This effect, as well as a delayed serum peak concentration in swallowed preparations, was observed in one recent study.[28]

Patients receiving oral transmucosal fentanyl citrate in this study removed and inserted the lozenge as desired. Thus, they were able to stop medication administration when adequate analgesia was achieved or in response to adverse effects. Although an optimal principle of desired pain control, self-titration could account for the lower

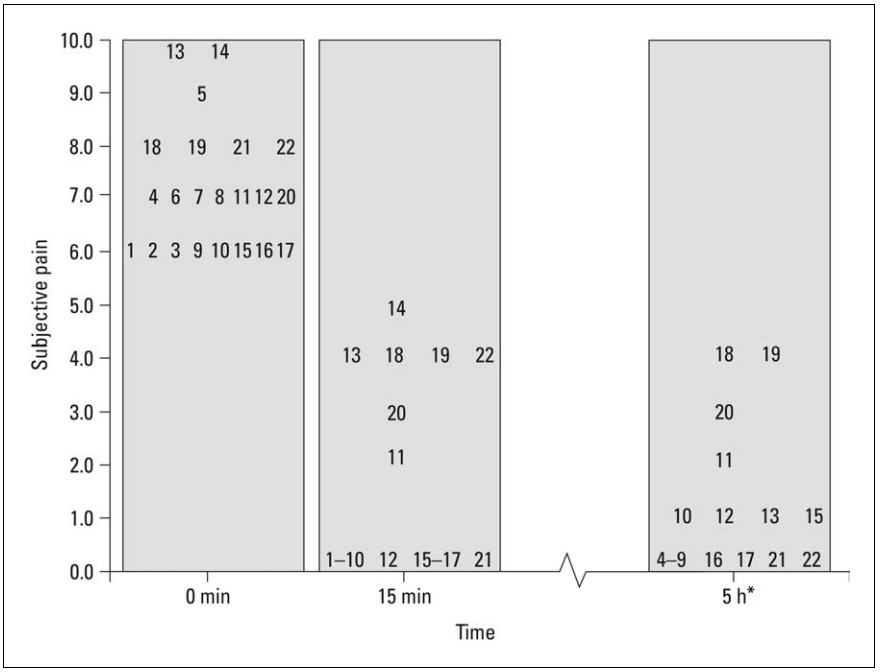

Figure.
*Casualty number plot of effect of 1,600 µg dose of oral transmucosal fentanyl citrate on subjective pain. The median pain rating at initial presentation was 7.0 (mean 7.18, SD 1.26, 95% CI 6.62 7.74, N=22). The median pain rating at 15 minutes after medication adminis tration was 1.0 (mean 1.41, SD 1.74, 95% CI 0.64 2.18, N=22), and the median pain rating at 5 hours after medication administration was 0.5 (mean 1.00, SD 1.37, 95% CI 0.32 1.68, N=18). Eight casualties (1, 2, 3, 13, 18, 19, 20, 21) experienced minor adverse effects, and 1 casualty (14) experienced a major adverse effect. *Data were not obtained for 4 casualties (1, 2, 3, 14) at the 5 hour mark. Three casualties (13, 14, 22) received additional pain medi cation before this time.*

adverse-effect profile observed in this study. Although viewed by the authors as an advantage of this medication, this type of administration may have limited our ability to observe the actual safety of the 1,600-μg dose. Additionally, provider control of titration for a measurable baseline minimum effective dose required for individual pain thresholds for specific injuries may necessitate a guideline that institutes multiple smaller doses through time.

In this study, minor adverse effects were seen in 36% of patients and were limited to pruritus, nausea, emesis, and lightheadedness. It should be noted that fatigue, emotion, heat, and map-of-the-earth tactical flight can autonomously invoke nausea and emesis, and most certainly these factors can synergistically prompt or exacerbate existing medication adverse effects. Most studies cite the frequency of pruritus at 50% to 60% (range 3% to 81%), vomiting at 40% (range 0% to 65%), and transient oxygen desaturation below 94% as rare (range 0% to 24%).[21] Major adverse effects can include respiratory depression, chest wall rigidity, and bradycardia. In this study, respiratory depression was observed in 1 patient, and no episodes of chest wall rigidity or nonphysiologic bradycardia were reported.

The injuries in this study resulted from blunt trauma and included strains, sprains, dislocations, and fractures. There were no individuals in the study population with penetrating trauma because many of these casualties required intravenous resuscitation and medication. Similarly, individuals with closed head injuries and severe spinal injuries with neurologic deficits were not included.

In 2002, the Centers for Disease Control and Prevention reported 4.3 million nonfatal sports and recreation-related injuries treated in US EDs.[37] Of those, 1.2 million (29.1%) injuries were sprains and strains, 881,000 (20.5%) injuries were fractures, and the most common body part to sustain injury was the ankle (516,000 [12.1%] injuries). Although only military injuries were evaluated in this study, similarities can be seen between the Centers for Disease Control and Prevention injury data and injury data depicted in this study.

Thus, the need for out-of-hospital pain management is definitely not limited to the military. Millions of people worldwide experience injuries every year that require out-of-hospital care and transport to EDs. However, according to Dachs,[38] recent studies note that out-of-hospital care providers continue to harbor non–evidence-based assumptions that lead to ineffective treatment of patients with severe pain. As observed in this study, medical personnel can target and rapidly administer analgesia in close proximity to the point of wounding to provide definitive pain control.

Oral transmucosal fentanyl citrate lozenges appear to be an acceptable pain management alternative for administering rapid-onset opiate analgesia in the out-of-hospital combat setting, and we recommend the continued use and exploration of an oral transmucosal fentanyl citrate clinical practice guideline for combat applications. Future application should include additional titration through multiple lower doses given sequentially as needed to delineate individual requirements for specific injuries, possibly reduce adverse effects, and further increase the margin for safety. Additionally, oral transmucosal fentanyl citrate should be considered for treatment of noncombat injuries that result from field-training exercises, parachuting, and other potentially hazardous military and paramilitary activities. Select out-of-hospital trauma resulting from falls, motor vehicle crashes, sporting events, and other causes could also potentially benefit from the use of oral transmucosal fentanyl citrate.

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